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RESEARCH ARTICLE

Can We Predict the Sites of the Recurrence of Ovarian Cancer by F-18 FDG PET/CT Depending on CA-125 Level?

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Abstract: ***Objectives*****:** The purpose of the study is predicting the sites of the recurrence with PET/CT by serum CA-125 level and detecting the cut-off value of CA-125 for metastatic ovarian cancer (OC) in comparison with Fluorine-18 FDG PET/CT.

Materials & Methods**:** For 38 patients with histological stage III-IV OC, F-18 FDG PET/CT studies (n=59) referred for suspicion of relapsing of OC were conducted. PET/CT images were assessed as positive/negative in 4 categories based on similar location as local recurrence, peritoneal metastasis, lymph node metastases and distant metastases. Patients were divided into five groups according to the levels of CA-125. The results of PET/CT imaging were compared with the level of CA-125.

Results**:** Recurrence was confirmed in all FDG-PET/CT studies. In 7 of them (11.9%) CA-125 levels were normal (mean: 18.9±5.9) whereas in 52 of them (88%) were high (mean: 433.9±798.3). Moderate but highly significant positive correlation between CA-125 level and the number of metastatic foci detected by PET/CT was found. There was no statistically significant difference between CA-125 level subgroups and metastatic sites. However, the difference between CA-125 levels and location of metastasis was statistically significant only for distant metastasis and peritoneal metastasis with moderate accuracy (71% and %66, respectively).

Conclusion**:** Since CA-125 has moderate but highly significant positive correlation with the number of metastatic foci, it is important in clinical management of OC patients. However, it may not predict the localization of the recurrence. When suspicious findings were reported at radiodiagnostic techniques in OC patients, FDG-PET is a useful technique for detecting recurrent ovarian carcer regardless of CA-125 level.

Keywords: Serum CA-125, metastatic ovarian cancer (OC), fluorine-18 FDG PET/CT, peritoneal metastasis, lymph node metastases, distant metastases.

1. INTRODUCTION

Ovarian cancer (OC) is the fifth most common malignancy and it is the leading cause of death among gynecologic malignancies in woman [1]. It has bad prognosis and diagnosed in advanced stages because it does not cause any earlier symptoms and there is no effective screening method for OC. Recurrence is seen in 70% of patients after treatment. Due to the aggresiveness of OC, imaging modalities and serum CA-125 levels are very important in follow up [2].

Cancer antigen (CA-125) is a mullerian channel differentiation antigen and it is secreted from epithelial cells of OC. It can also be secreted from other epihelial cells in body [3]. Serum CA-125 levels increase before the symptoms of recurrence. However, it does not give information about prognosis and localization of recurrences and metastases [1]. Moreover, its level does not increase in all metastatic patients [1, 4, 5].

Detection and exact localization of recurrent lesions are critical for guiding management and determining the proper therapeutic approach, which may prolong survival [4-6]. Because of its high sensitivity and specificity compared with those of conventional techniques such as computed tomography (CT) and magnetic resonance (MR) imaging, Fluorine-18 fluorodeoxyglucose (F-18 FDG) positron emission tomography combined with CT (PET/CT) is useful for detection of recurrent or residual ovarian cancer and for monitoring response to therapy.

PET/CT has the highest diagnostic accuracy among other imaging modalities for detecting tumoral lesions [6]. It also

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affects treatment planning and it is stated in literature that PET/CT changes treatment strategies for above 60% of patients [7, 8].

In our country, for OC, elevation in serum CA-125 levels is the only indication for examining whole body PET/CT and this indication is stated in PET/CT imaging guideline of Social Security Institution (Supplement 2/D-1). However, it is elevated (>35U/ml) in 80% of ovarian cancer cases even at initial stage [9], in the late process, the sensitivity of elevated levels is reduced in only 50% of patients. The specificity of CA-125 is also limited due to its association with benign diseases as fibroids, endometriosis and physiological conditions as menstruation [10, 11].

Prostate cancer patients with serum levels of prostate specific antigen (PSA) above 20 ng/ml are defined as high risk for metastasis and they must be investigated. Even though there is no pathological uptake at routine metastatic screening method "bone scintigraphy", advanced imaging methods must be considered. And bone metastasis is strongly suspected when serum levels are above 100 ng/ml independent of imaging modalities [12]. Similar to this work-up, there is no cut-off serum levels of CA125 in OC patients to guide for appropriate imaging modalities or therapy regimens [13].

Aim of this study was to evaluate the sites of the recurrence based on CA-125 level and to predict the sites of metastatic lesions with PET/CT examination in comparison with CA-125 level in patients with suspicion of recurrent OC.

2. MATERIAL AND METHODS

2.1. Patient Selection

This retrospective study was approved by our institutional Ethical Committee and informed consent was waived. The PET/CT reports of 5123 images from our clinic between January-2012 and January-2016 were searched for the word "OC" in the impression. We found 100 OC patients' images. Of those 41 images were excluded and 59 (59%) images of 38 patients were further analyzed. Average age was 56.8 years (range 35-77 years). All patients' histological diagnosis was high-grade serous carcinoma. 17 patients (44.7%) were stage 3b, 19 patients (50%) were stage 3c and 2 patients (5.3%) were stage 4. The exclusion criteria was patients who were stage I-II, patients who received chemotherapy and/or radioterapy just before imaging, patients who had normal PET/CT findings and patients who were under 18 years old. Patients who had positive FDG PET/CT findings, who were stage III and IV and, who had radical treatment for ovarian cancer (chemotherapy, surgery or combination) and whom CA-125 level was increased or normal CA-125 level with suspicious findings at conventional radiodiagnostic techniques were included in study. Serum CA-125 level measurement and PET/CT examination were performed with a maximum interval of 30 days.

2.2. F-18 FDG PET/CT Protocol

PET images were acquired using a combined PET/CT scanner (Discovery 600 PET/CT, GE Medical Systems, USA). Each patient fasted for at least 6 h before imaging. F-18 FDG [370–703 MBq (10–19 mCi)] was administered to patients with blood glucose levels lower than 150 mg/dl. After topogram images, unenhanced low-dose CT scan (automated dose modulation (50-250mA), 120 kV) and then PET images from the vertex to 1/3 of the upper portion of the thigh were acquired. PET data was acquired in 3D mode with scan duration of 3 min per bed position. The data were transferred via the Digital Imaging and Communications in Medicine (DICOM) protocol to a processing Workstation (AW Volumeshare 5, GE Medical Systems S.C.S, France). Two nuclear medicine physicians retrospectively reviewed the PET/CT images.

2.3. Data Analysis

Visual analyses were performed by a consensus of two clinical information-blinded experienced nuclear medicine physician, based on HU units, morphologic appearance and with FDG uptake higher than that of the liver for >10mm lesion [14] and that of the adjacent structures for <10mm lesions [6] corresponding to an abnormal lesion showed on CT. All patients had a clinical and radiodiagnostic follow up of at least 12 months (maximum 5 years) following the F-18 FDG PET/CT scan. During follow up, since all patients were metastatic, there were no histological proof for suspected metastatic regions, while all patients performed clinical, conventional, ultrasonographic, and laboratory evaluatios. Also diagnosis of metastatic lesions was based on interval growth or reduction after chemotherapy during follow up. Cervical, mediastinal lymph nodes and <1cm lung nodules that remained unchanged for over 1 year was the standard used to diagnose benign lesions [15].

First, each positive PET/CT image was assessed as positive or negative in 12 categories: Tumor local recurrence, abdominal metastasis (gastric, celiac, pancreatic, portal, hepatic, splenic lymphatic region), peritoneal implants, peritonitis carsinomatosis, paraaotic and paracaval lymphatic chain, pelvic metastasis (iliac, obturatuar, gluteal, inguinal lymphatic region), cervical, mediastinal, lung, liver, spleen and bone. Subsequently, for obtaining enough numerous groups of patients to be able to perform a statistical analysis, we grouped the regions based on similar location and additionally assessed as positive or negative in 4 categories: (I) local recurrence (in the pelvis), (II) peritoneal metastasis (peritoneal implants, peritonitis carsinomatosis), (III) lymph node metastases (paraaortic/paracaval lymphatic chain and abdominal lymphatic sites) and (IV) distant metastases (cervical, mediastinal, lung, liver, spleen and bone) [5, 6]. In this category, the F-18 FDG uptake patterns indicative of peritoneal metastasis were: (a) focal nodular F-18 FDG uptake detected on peritoneal surfaces, excluding lymph nodes; (b) diffuse F-18 FDG uptake in the superficial abdominal planes which appeared thickened; (c) diffuse F-18 FDG uptake in the ascitic fluid [16].

On the basis of serum CA-125 levels, first patients were divided into 2 groups: normal or elevated if ≤35 or >35 U/ml [16, 17] but since there were heterogeneous distribution based on this classification, subsequently for obtaining enough numerous groups of patients to be able to perform a statistical analysis, patients were divided into five groups accordingly to the levels of CA-125 levels as (I) ≤35 U/mL, (II) 36–75 U/mL, (III) 76–150 U/mL, (IV) 151–350 U/mL

and (V) >350 U/mL as in literature [5], and the metastatic regions observed at F-18 FDG PET/CT were analysed group by group.

2.4. Statistical Analysis

Difference between values of serum CA-125 levels in PET/CT positive and negative patients for each region defined according to the location of metastasis was compared using the Mann-Whitney U-Test. ROC curve analysis was carried out for serum CA-125 level to determine the best cut-off level of CA-125 to predict positive PET/CT result for statistically significant locations. A student-t-test was used between CA-125 levels in groups and PET/CT positive and negative patients for each region defined according to the location of metastasis. While investigating the associations between the number of metastatic foci and CA-125 level, the correlation coefficients and their significance were calculated using the Spearmen test. A p-value less than 0.05 was considered significant. All statistical analyses were carried out using SPSS software (Ver 22.0; SPSS Inc., Chicago, Illinois, USA).

3. RESULTS

All patients had positive F-18 FDG PET/CT findings. The median level of serum CA-125 was 112.6 (range 11.5-4995 U/mL, SD: 760.8). 7 studies had normal CA-125, 52 studies had >35 U/mL CA-125 level. According to the 5 subgroups based on CA-125 level, 7, 11, 15, 11 and 15 studies had CA-125 level as ≤35 U/mL, 36–75 U/mL, 76-150 U/mL, 151–350 U/mL and >350 U/mL, respectively (Table **1**). There was no statistically significant difference in between CA-125 level subgroups and metastatic sites (Table **2**). PET/CT positive and negative images for each region defined according to the location of metastasis were shown at Table **2**.

The difference between CA-125 level and location of metastasis was statistically significant only for distant metastasis and peritoneal metastasis ($p<0.05$), whereas no statistically significance was observed for local recurrence and lymph node metastasis (Table **3**).

Table 1. Number of images based on CA-125 level.

CA-125 Level	No. of Images (%) (n=59)
≤35 U/mL	7 (11.9%)
36-75 U/mL	11 (18.6%)
76–150 U/mL	15 (25.4%)
151–350 U/mL	11 (18.6%)
>350 U/mL	15 (25.4%)

Mean CA-125 level in patients with positive distant metastasis was 570±178.7 U/mL whereas that of patients with negative distant metastasis was 179.5±46.2 U/mL ($p<0.05$). Also in patients with positive and negative peritoneal metastasis, mean CA-125 level was 582.9±173.9 U/mL and 149.8±34 U/mL, respectively ($p<0.05$) (Table **3**). For statistically significant predicted metastatic sites, ROC analysis was performed which revealed that the optimal cut-off value for CA-125 to predict posivite peritoneal metastasis was 194.5 U/mL with accuracy of 66% (AUC:0.697, %95 CI:0.564-0.830) and to predict positive distant metastasis was 106.7 U/mL with accuracy of 71% (AUC:0.674, %95 CI:0.532-0.816). These AUC values demostrated weak predicting power of this marker (Figs. **1** and **2**).

On the other hand, moderate but highly significant positive correlation between CA-125 levels and the number of metastatic foci detected by PET/CT was found ($r=0.482$, $p=0.000$). Of note, in one excluded patient whom CA-125 level was >10000 U/mL and observed multiple metastaic foci all through out the body was stage 1b at the initial stage.

4. DISCUSSION

Since OC has a high risk of recurrence, monitoring of those patients plays an essential role in management. CA-125 level is an important serum marker for the detection of recurrence of OC [3] with a good overall accuracy (80%) but a low negative predictive value (NPV) [18, 19]. Also it does

Table 2. CA-125 levels in groups defined according to the location of the metastasis.

Metastatic Sites		CA-125 Level (U/mL)					P value*
		≤35	36-75	76–150	151–350	>350	
Local Recurrence	Positive (n=23)	2 (8.7%)	5 (21.7%)	5 (21.7%)	3 (13%)	8 (34.8%)	>0.05
	Negative (n=36)	5 (13.9%)	6 (16.7%)	10 (27.8%)	8 (22.2%)	7 (19.4%)	
Lymph Nodes	Positive (n=47)	3 (6.4%)	10 (21.3%)	12 (25.5%)	10 (21.3%)	12 (25.5%)	>0.05
	Negative (n=12)	4 (33.3%)	1 (8.3%)	3 (25%)	1 (8.3%)	3 (25%)	
Peritoneal Metastasis	Positive (n=32)	2 (6.3%)	4 (12.5%)	9 (28.1%)	5 (15.6%)	12 (37.5%)	>0.05
	Negative (n=27)	5 (18.5%)	7 (25.9%)	6 (22.2%)	6 (22.2%)	3 (11.1%)	
Distant Metastasis	Positive (n=31)	4 (12.9%)	3 (9.7%)	6 (19.4%)	7 (22.6%)	11 (35.5%)	>0.05
	Negative (n=28)	3 (10.7%)	8 (28.6%)	9 (32.1%)	4 (14.3%)	4 (14.3%)	

*Student-t-test.

Table 3. CA-125 levels according to the location of metastasis.

Metastatic Sites		CA-125 Level		P value[#]
		Mean±SD	Median (min-max)	
Local Recurrence	Positive (n=23)	441.3 ± 133.9	127.1 (18-2338.10)	p=0.312
	Negative (n=36)	348.5 ± 139	105.4 (11.5-4995)	
Lymph Nodes	Positive (n=47)	433.5 ± 122.5	114.1 (17.2-4995)	p=0.221
	Negative (n=12)	193.3 ± 64.3	95.6 (11.5-630.1)	
Peritoneal Metastasis	Positive (n=32)	582.9 ± 173.9	243.6 (15.2-4995)	p=0.022*
	Negative (n=27)	149.8 ± 34	98 (11.5-785.4)	
Distant Metastasis	Positive (n=31)	570 ± 178.7	199.7 (11.5-4995)	p=0.01*
	Negative (n=28)	179.5 ± 46.2	89.4 (15.2-1099.8)	

[#]Mann-Whitney U-Test.

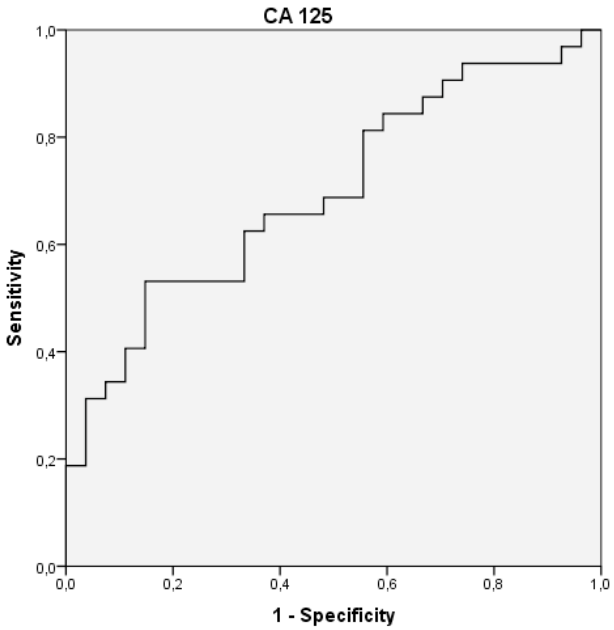

Fig. (1). The ROC analysis demostrated an optimal cut-off value for CA-125 of 194.5, with an AUC of 0.697 in the prediction of peritoneal metastasis with sensitivity of 53%, specificity of 82% and accuracy of 66%.

not give information about prognosis and localization of recurrences and metastases [1, 13] and because of low NPV, normal values can not exclude the presence of active disease. Therefore, besides the serum markers, a close follow-up is critical with the help of imaging scans.

In detecting recurrence or metastasis, PET/CT has the highest diagnostic accuracy among the other imaging modalities [6]. It may provide the management of the patients in above 50% of cases [7, 17]. In our country, PET/CT is mostly recommended for patients of raised CA-125 levels as in most country. However, it is not clear whether there is a CA-125 cut-off level above which the detection rate of FDG PET/CT is significant so that the procedure becomes cost-effective.

In accordance with the literature [1, 4, 5, 13], although all PET/CT images were positive in our study, 7 PET/CT scan had normal CA-125 level (<35 U/mL) and so could be overlooked unless PET/CT was performed (Fig. **3**). Fularz *et al*. reported similar results [13]. They showed 10 out of 42 patients with normal CA-125 level who had positive PET/CT results.

There are many studies that have evaluated the clinical role of the combination of FDG-PET and CA-125 levels in the detection of recurrence or the contribution of FDG-PET to the diagnosis and clinical management of patients who were suspected of recurrent ovarian carcinoma. To the best of our knowledge, there is only one study investigating the directional feature of the CA-125 level to show the recurrence sites detected by PET/CT at 68 patients [13]. According to that study, CA-125 level does not depend on the localization of the relapsing ovarian cancer. Similar to this study, we also found that the comparison of CA-125 levels in

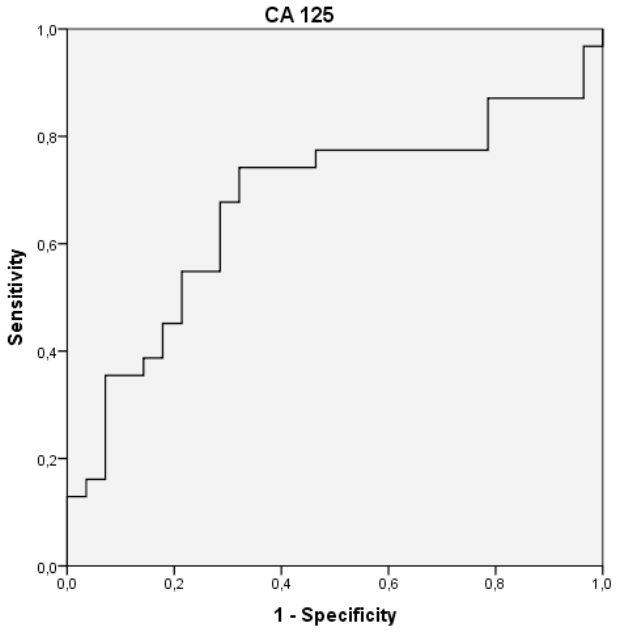

Fig. (2). The ROC analysis demostrated an optimal cut-off value for CA-125 of 106.7 U/mL, with an AUC of 0.674 in the prediction of distant metastasis with sensitivity of 74%, specificity of 68% and accuracy of 71%.

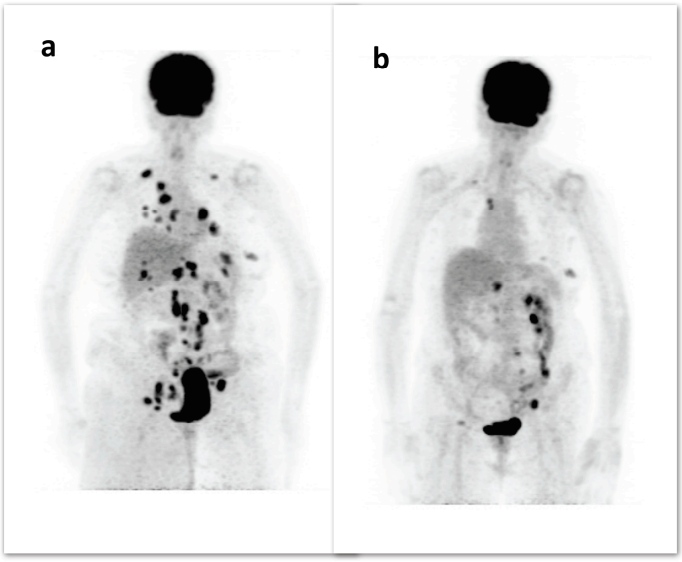

Fig. (3). A patient (68 y.o.) with serum CA-125 level: 18 mL/U when referred to our clinic **(a)** and after 6 cycles of chemotherapy **(b)**. **a**) PET maximal intensity projection (MIP) image showing foci of increased uptake of ^{18}F-FDG at bilateral supraclavicular region, mediastinum, lung parenchyma, paraaortic and paracaval lymphatic chain and peritoneal regions in the pelvis. **b)** PET MIP image after 6 cycles of chemotherapy showing significant regression of increased uptake of ^{18}F-FDG lesions at supraclavikular, mediastinum, lung parenchyma, paraaortic and paracaval lymphatic chain and peritoneal regions in the pelvis.

groups and location of pathological lesions separated based on PET/CT images showed no statistically significant difference. But instead of comparison of CA-125 levels in groups, when we investigated the difference of CA-125 levels with the location of metastasis, it was statistically significant only for distant metastasis and peritoneal metastasis, whereas no statistical significance was observed for local recurrence and lymph node metastasis. Rubini *et al.* [16] investigated the role of PET/CT in diagnosing the peritoneal carcinomatosis as compared to contrast-enhanced CT and CA-125 levels at 79 patients and found that overall sensitivity and specificity of PET/CT was 85% and 92.3%, respectively, whereas when they compared FDG PET/CT images with CA-125 levels at 35 patients, they found the sensitivity of CA-125 was 93.3% while specificity was 33.3% for detecting peritoneal carsinomatosis. In our opinion, Rubini's study had a limitation as they investigated a heterogeneous histological diagnosis group of patients those consists of serous, mucinous, papillar, borderline, endometrioid and epithelioid pattern of ovarian cancer.

In our study, as it was expected, there was moderate but highly significant positive correlation between CA-125 levels and the number of metastatic foci detected by

PET/CT. Also Palomar *et al*. [5] found similar results. They showed the higher the level of CA-125, the higher the probability to detect the site of disease. They also found that although detection rate is significantly higher in groups of patients with CA-125 >30 U/mL (81-96%), a significant number of patients (approximately 10%) with very high levels of CA-125, had a negative PET/CT, despite the high detection rate of this technique. They concluded that the detection rate is stable when the marker level is above the absolute value. Also it is our opinion that, when extensive involvement of milimetric focal peritoneal implants exist concomitant with high CA-125 level, this may be misinterpreted as physiological bowel FDG uptake with a lower probability to be detected by PET/CT system due to spatial resolution limitation.

It is clear that CA-125 is highly associated to serous type of cancer, but this relation is not so strong for mucinous tumors [20]. Palomar *et al.* [5] investigated 175 patients with ovarian cancer with heterogeneous histological subtypes. In addition, they found nonsignificant relative difference in the values of CA-125 levels among the mucinous and serous type of tumour. They reported mean CA-125 level as 77.8 U/m L and 123.7 U/mL for mucinous and serous type, respectively and proportionally with this result, FDG PET/CT detection rate was 66.6% for mucinous type and 74.2% for serous histology. Therefore before the use of FDG PET/CT for the purpose of accurate recurrence localization detection based on CA-125 level, we must consider that the histological diagnosis of the patient must be serous type. In our highly selective study group, all patients had a same histological type of tumor, which is serous histology.

With the use of ROC analysis, we found that the most adequate cut-off value of CA125 in predicting positive peritoneal metastasis was 194.5 U/ml with the sensitivity and specificity of 53% and 86%, respectively and for predicting distant metastasis the adequate cut-off value was 106.7 U/mL with the the sensitivity and specificity of 74% and 68%, respectively but both in low accuracy. Fularz *et al*. [13] found that the most adequate cut-off value of CA-125 in predicting positive PET/CT result independently of metastatic location was 17.6 U/ml with the sensitivity and specificity of 90.9% and 80.0%, respectively. Also Palomar *et al*. [5] reported similar results in their study. They also revealed the optimal cut-off value of 18 U/ml, achieving 85.6% positive PET/CT results in a group with CA-125 level above this threshold. It is worth emphasizing that, the reason for the large difference between our values and these two studies was that, they did not investigate the metastic sites based on the location, they only analyzed the PET/CT results overall as positive or negative.

PET/CT may yield false-negative results in patients with small, necrotic, mucinous, cystic, or low-grade tumors. In addition, in the posttherapy setting, inflammatory and infectious processes may lead to false-positive PET/CT results. However in our study, we only included the patients who had serous type and high grade tumour and who had not been scanned just after the operation and therefore we thought that we excluded those drawbacks.

Our retrospective study had some limitations. We did not include the patients with negative PET/CT findings accompanying with high CA-125 serum level. The reason for doing so is that, the aim of our study was not correlated with the PET/CT findings with serum CA-125 level, and not to investigate the sensitivity of PET/CT based on CA-125 level. We aimed to predict the sites of the recurrence with PET/CT by CA-125 level and therefore we only included the patients with positive PET/CT findings. Second limitation was the lack of pathological confirmation of all sites of abnormal FDG uptake. It would not have been possible or ethical to confirm all sites of abnormal FDG uptake in patients with more than one lesions identified and the guidelines considering the instrumental clinical assessment are sufficient for restaging the patients who have already been treated for OC [7, 16].

CONCLUSION

According to our research, CA-125 level may help to detect the advance stage of OC patients; despite that CA-125 level is poorly determinant for prediction of recurrence localization. This confirms the great role of PET/CT in detecting tumour recurrence in order to adequately manage patient's treatment. Moreover, it can be also helpful in reducing the incidence of laparatomies and better select patients to whom peritoneal biopsy is either inappropriate or unavailable. In clinical practice, when we are faced with CA-125 level above 194.5 and 106.7 U/mL, we should suspect to peritoneal metastasis and distant metastasis, respectively. To confirm those levels, further studies are needed for each pathological subtype with more patients.

FDG-PET is a useful technique for detecting recurrent ovarian carcinoma suspected either by elevated or normal serum marker levels with normal or equivocal results in the morphologic imaging techniques. It was concluded that the combination of FDG-PET and CA-125 levels is useful for the accurate detection of recurrence.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

All procedures performed in the study were in accordance with the ethical standards of the Instutional Committee and with the 1964 Helsinki declaration and later amendments or comparable ethical standarts.

HUMAN AND ANIMAL RIGHTS

No Animals/Humans were used for studies that are base of this research.

CONSENT FOR PUBLICATION

Not applicable.

CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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Declared none.

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